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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

de Baar et al.

Serial No.: 09/785,881

Filed: February 16, 2001

For: REDUCING BACKGROUND IN HYBRIDIZATION REACTIONS

Examiner: A. Chakrabarti, Ph.D.

Group Art Unit: 1655

Attorney Docket No.: 4760US

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Amendment

Box Non-Fee Amendment
Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action mailed November 7, 2001, please amend the referenced application as follows:

IN THE CLAIMS

C1

1. (Amended) A method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous probes, wherein at least one of the two homologous probes is a non-linear probe, said method comprising:

introducing a mismatch with an intended target sequence in said non-linear probe; and

conducting a hybridization reaction using said at least two homologous probes, thereby reducing the background signals of the hybridization reaction.

C1

2. (Amended) A method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous target sequences, said method comprising:

providing for an intended mismatch between at least one of the two homologous target sequences and at least one non-linear probe; and

conducting a hybridization reaction using said at least two homologous target sequences, thereby reducing the background signals of the hybridization reaction.

C2

16. (Amended) A method of conducting a hybridization reaction comprising:

mixing a set of homologous probes for detecting at least one allelic variant of a nucleic acid, wherein at least one of said set of homologous probes is non-linear, said set of homologous probes comprising at least one sequence completely complementary to and specific for one of the allelic variants of said nucleic acid, except for a specific mismatch located upstream, downstream or both upstream and downstream from the site of variation;

detecting variants of the nucleic acids; and

using the set of homologous probes to conduct the hybridization reaction.

Remarks

The office action mailed November 7, 2001 has been received and reviewed. Claims 1 through 9, 16 through 18, and 21 through 25 are pending. All claims are rejected. The claims are to be amended as herein set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. Examiner Interview:

Applicants would like to thank the examiner and his supervisor for the courtesy extended during the interview of January 18, 2002. Applicants found the interview extremely useful in understanding the issues as evidenced by the interview summary (Paper No. 10),

> "Applicant will explain claim 1, especially the phrase 'homologous probes' to make the invention more clear. Applicant's amendment will be considered favorably."

2. 35 U.S.C. § 112, 2nd ¶:

Claims 1-9 and 21-25 were rejected as assertedly being indefinite for failing to include a process step relating back to the preamble. Applicants have amended claims 1 and 2 to include such a process step and therefore respectfully request withdrawal of the rejections.

3. 35 U.S.C. § 103:

The pending claims were rejected as being obvious over various combinations of U.S. Patent 4,683,194 to Saiki et al. ("Saiki"), U.S. Patent 5,607,834 to Bagwell et al., a journal article to Guo et al., and U.S. Patent 6,027,880 to Cronin et al. Saiki was the primary reference. (Office Action, pages 4-10). Applicants respectfully traverse the rejection.

As discussed at the interview of January 18, 2002, none of the references are believed to disclose the the homologous probes of the instantly claimed invention. As used in the instant application, at paragraph nos. 0007 through 0010:

> "at least two of the probes comprise an identical sequence except for the variation of the point mutation and possibly the site of the mismatch. This does not mean that the sequences must be identical over the whole of the molecule, but that they are identical in the part where hybridization should occur. This is a situation in which false positives are a significant risk. The mismatch should comprise as many nucleotides as necessary to significantly lower the

background, but not so many nucleotides that the probe having the exact match for the allelic variation (point mutation) has a significantly lower binding affinity. The number depends of course on the length of the probe and the base composition of the probe. Typically no more than 10 percent of the probe should be mismatch, preferably less than 5%, and especially about 1-3 nucleotides in a 20 nucleotide probe or the corresponding percentage in a shorter or longer probe. Thus, in a further embodiment the invention provides a method wherein the mismatch comprises 1-3 nucleotides. For the same reasons as mentioned above, the mismatch should be located not too close, but also not too far away from the actual site of variation. Typically in a 20 nucleotide probe it should be located between 2 and 5 nucleotides from the site of variation. Thus, in a further embodiment the invention provides a method wherein the mismatch is located between 2 and 20 nucleotides up-or downstream of the point mutation.

[0008] Probe length is not really critical. Conventional probe lengths are suitable. Usually probes should not exceed 50 nucleotides and should not be less than 15 nucleotides, with a good average at about 20 nucleotides. Thus, in yet another embodiment the invention provides a method wherein at least one non-linear probe has a length of about 15-50 nucleotides. As stated above, a label is typically applied for detection of bound (sometimes unbound) probe. The label may be any conventional label, and it may be attached to the probe or the hybridized complex at any suitable time. Thus, in yet another embodiment, the invention provides a method wherein at least one of the mixed homologous non-linear probes is provided with a detectable moiety. . . .

[0009] Sets of probes designed for the methods of the present invention are also provided by the invention. Thus, the invention provides *e.g.*, a set of mixed homologous probes for detection of at least one allelic variant of a nucleic acid family, wherein at least one of the probes is non-linear, the probes comprise sequences that are completely complementary to and are specific for one of the allelic variants of the family, except for a specific mismatch located upstream and/or downstream from the site of variation.

[0010] The invention further provides a set of mixed homologous primers, wherein at least two of the probes comprise an identical sequence except for the variation of a point mutation and possibly the site of the mismatch, preferably a set wherein the mismatch comprises 1-3 nucleotides. The reasons for the design of the sets of primers have been explained above and will become more apparent from the experimental part. The invention also provides a set wherein the mismatch is located 2-20 nucleotides upstream or downstream of the point mutation, whereby the probes typically have lengths between 15 and 50 nucleotides."

As shown by the inventors in the examples, such probes act to reduce background noise in the hybridization reaction. (Specification, pp. 7-9 and FIG. 1).

In contrast to applicants' homologous probes, Saika teaches the use of an "oligomer which

is complementary to the probe, but has at least one base pair mismatch within each restriction site being detected, so that the labeled probe not already hybridized to the nucleic acid will hybridize to the blocking oligomer . . . ." (Saika, col. 6, line 68 through col. 7, line 5, emphasis added). A complementary probe is not a homologous probe as used in the instant application.

None of the other references of record are believed to disclose the claimed use of homologous probes either, and, accordingly, applicants respectfully request withdrawal of the obviousness rejection based on these references.

4. Priority Document:

The certified copy of the priority document EP 00200549.4 filed February 17, 2000 was sent as a separate communication which should perfect the priority claim for the instant application.

Conclusion

The pending claims are believed to be in condition for allowance. If, however, questions should exist after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address / telephone number given herein.

Respectfully submitted,

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